A PAX-8-positive Female Urethra Adenocarcinoma: A Case Report with Diagnostic Challenges in Intestinal-Type Adenocarcinoma

Mary Torrez, MD, Robert Allen, BS, Jain Zhou, MD, PhD
Department of Pathology, University of New Mexico Health Sciences Center, Albuquerque NM

Background
- Female urethral carcinoma is rare, representing 0.02% of all women’s cancers and <1% of cancers in the female genitourinary tract.
- The most common histologic type is squamous cell carcinoma (70% of all cases), followed by transitional cell carcinoma (20%) and adenocarcinoma (10%).
- The two primary histologic subtypes of adenocarcinoma of the urethra are clear cell and columnar/mucinous (“intestinal”); the latter being extremely rare.
- Female urethral adenocarcinoma (FUA) exhibiting colonic adenocarcinoma features has only been described once previously, to our knowledge.
- Furthermore, PAX-8 immunexpression in this entity has not been reported.
- Herein, we report an intestinal-type FUA that developed from inflammation-related metaplasia in urethral diverticulum with positive PAX-8 staining.

Case History
- 64-year-old female with a 32-pack-year history of tobacco use was found to have multiple pulmonary nodules on computed tomography (CT) scan (Fig 1A).

Findings
- Needle core biopsy of pulmonary nodules demonstrated moderately differentiated adenocarcinoma (Fig 2A); the tumor cells were positive for CK7, CK20 (Fig 1B), SAT-B2, and PAX-8 (Fig 1C) and negative for TTF-1/Napsin (Fig 1D) and ER; GATA-3 staining appeared cytoplasmic.
- Diagnostic considerations included gastrointestinal as a primary site, and the positive PAX-8 immunexpression raised the possibility of a gynecologic/Mullerian primary.
- Subsequent colonoscopy and imaging showed no evidence of colorectal or gynecologic tumors.
- The patient began having hematuria with intermittent urinary retention, and cystoscopy showed a 4 x 3 cm mass involving the bladder neck circumferentially and invading into the vaginal wall.
- Urethral and vaginal tumor biopsies were performed. Morphologic examination of the urethral biopsy demonstrated intestinal metaplasia of squamous mucosa with transition from a mature to dysplastic phenotype (Fig 3A) where the adenocarcinoma originated from. The vaginal wall biopsy showed the same morphology.
- The urethral and vaginal wall biopsies showed a similar immunophenotype as the pulmonary nodule biopsy: positive for CK7, CK20, CDX2 (Fig 3B), b-catenin (membrane stain), CEA, patchy expression of SATB2 (Fig 3C) and PAX-8 (Fig 3D), and negative for TTF-1, p16, ER, Vimentin and GATA-3.

Discussion
- In this case, we describe a rare case of intestinal-type primary urethral adenocarcinoma that developed from inflammation-related metaplasia in urethral diverticulum with PAX-8 expression.
- Because of the immunophenotype, it was prudent that other sites, including colorectal and gynecologic/Mullerian tumors, were excluded.
- The patient presented with advanced disease, with metastasis to the lungs, exemplifying the aggressive nature of this particular entity.
- The patient was started on chemotherapy and eventually underwent palliative radiation for bone metastasis.
- FUA is a rare, aggressive tumor, and the origin remains unclear. Many authors have suggested that FUA originates in Skene’s glands; however FUA may arise from other pararectal structures.
- The vague symptomatology often leads to a delay in diagnosis in most patients, and the prognosis is poor in advanced stage disease.
- Furthermore, because of the disease rarity, there are no strict guidelines regarding treatment modality.

Fig 1A. CT shows multiple small, bilateral pulmonary nodules, the largest measuring 6 mm.

Fig 2. A. Histology showed adenocarcinoma with enteric differentiation. B. CK20 was strongly and diffusely positive. C. PAX-8 was diffusely positive with areas of both weak and strong staining. D. TTF-1/Napsin was negative, ruling out a pulmonary primary.

Fig 3. A. Histology showed squamous mucosa with intestinal metaplasia where adenocarcinoma originated. B-C. CDX2 and SATB2, supportive of an intestinal-type adenocarcinoma. D. PAX-8 remained positive on both urethral and vaginal biopsies.

References